

# Use of C-Reactive Protein in Minimizing Antibiotic Exposure: Experience With Infants Initially Admitted to a Well-Baby Nursery

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**ABSTRACT.** *Objective.* To evaluate the use of a clinical pathway for neonatal sepsis in decisions about initiating and continuing antibiotic treatment.

*Setting.* A district hospital primarily served by private pediatricians practicing in a managed care environment.

*Patients and Laboratory Tests.* All infants admitted to the well-baby nursery in 1997–1998 were eligible for this study. Infants born with a variety of risk factors (eg, borderline prematurity, membranes ruptured for over 18 hours, mother positive for group B streptococcus [GBS], and maternal fever) or clinical manifestations suggesting possible infection (either clinical signs or persistent hypoglycemia) were evaluated with white blood cell count, differential, and C-reactive protein (CRP) soon after birth and 12 hours later. Decisions to transfer to the neonatal intensive care unit and to treat with antibiotics were based on abnormal laboratory test results, particularly an increased level of CRP (>1 mg/dL), persistent hypoglycemia, or clinical signs. Discontinuation of antibiotic treatment was primarily based on return to normal of the CRP.

*Results.* Of 8299 live births, 7562 initially went to the well-baby nursery. Evaluation occurred in 1894 (25%) and 425 were transferred to the neonatal intensive care unit. In 162, antibiotics were discontinued within 48 hours. The majority were treated for 3 to 5 days, with only 19 (3 with GBS sepsis) treated for 6 days or more. There were 216 infants transferred because of risk factors and 209 because of clinical findings. Peak CRP primarily determined the duration of antibiotic treatment, with the mean peak CRP rising from 2.8 mg/dL in those treated for 3 days, to 3.8, 4.3, 8.4, 8.9, and 13.7 mg/dL in those treated for 4, 5, 6, 7, or >7 days, respectively. The mean duration of treatment was 3.1 days. No infant initially treated with antibiotics and discharged when the CRP returned to normal was readmitted within the next month. No infant with normal values on the sepsis screen was readmitted within 1 month with evidence of bacterial infection, but 1 infant with no risk factors was readmitted at 22 days of age with GBS sepsis and meningitis.

*Conclusions.* Using a clinical pathway for neonatal sepsis, which is based primarily on CRP determinations, can minimize antibiotic exposure and shorten hospital stays. *Pediatrics* 2000;106(1). URL: <http://www.pediatrics.org/cgi/content/full/106/1/e4>; *C-reactive protein, newborn infant, antibiotics, sepsis, group B streptococcus.*

ABBREVIATIONS. GBS, group B streptococcus(al); NICU, neonatal intensive care unit; CBC, complete blood count; CRP, C-reactive protein; WBC, white blood cell.

Neonatal sepsis remains an important diagnostic consideration in many infants, either because of risk factors or clinical manifestations associated with bacterial infection.<sup>1,2</sup> In recent years, the ability to make a definitive diagnosis of sepsis has been complicated not only by difficulties in obtaining large enough samples to detect positive blood culture results, but also by increasing use of prenatal antibiotics administered to the mother. This increased use of antibiotics is directed primarily at the prevention of group B streptococcal (GBS) infection and seems to have had some success.<sup>3</sup> However, it increases the difficulty for those clinicians caring for newborn infants, because positive blood culture results are even more difficult to obtain, so a definitive diagnosis of sepsis cannot be made. In addition, false-positive blood cultures secondary to contamination may be encountered. These may be distinguished by determining serial CRP levels.<sup>4,5</sup>

In preterm infants, who are routinely admitted to a neonatal intensive care unit (NICU), the infant can be evaluated and treated with little additional cost. In contrast, term infants are unlikely to be admitted to the NICU and there are economic pressures to discharge them sooner rather than later, particularly with vaginal deliveries. The clinician's dilemma is: "Which infants need antibiotic treatment and for how long should they be treated?"

Different strategies have been adopted in different institutions, with some of the variability attributable to the population being served. We report our experience in a district hospital, primarily served by private pediatricians practicing in a managed care environment, using a clinical pathway for neonatal sepsis.

## METHODS

This observational study was performed at El Camino Hospital, Mountain View, California, for the calendar years 1997 and 1998. The clinical pathway for neonatal sepsis was introduced ~1 year earlier after development by the Department of Pediatrics and approval of the executive committee of the medical staff of the hospital. Consequently, it was not submitted to the institutional review board of the hospital, and individual parental consent was not obtained. Obstetricians adopted a more aggressive approach to the use of prenatal antibiotics from June 1996, after publication of recommendations for the prevention of GSB infection.<sup>6</sup> For much of 1997, term infants born by vaginal delivery were discharged at ~24 hours of age, although this was closer to 48 hours

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during the last 3 months of the year and during 1998, after legislation had been introduced to mandate longer stays.

Risk factors that initiated evaluation on the clinical pathway included unexplained preterm labor at 35 to 37 weeks' gestation, rupture of membranes for >18 hours (nearly all of them received prenatal antibiotics), mother GBS-positive and given antibiotics, maternal fever (>38.0°C or >38.5°C if epidural anesthesia for >6 hours), fetal tachycardia (>180 beats/minute), and meconium-stained amniotic fluid without good explanation (eg, growth-retarded fetus, infarcted placenta, or postterm delivery). Clinical manifestations included tachypnea, dyspnea, temperature instability or fever beyond 4 hours of age, apneic or cyanotic episodes, poor perfusion, lethargy, or unexplained hypoglycemia. Data were collected prospectively.

With any of these risk factors or clinical manifestations, a complete blood count (CBC) and serum concentration of C-reactive protein (CRP) were determined immediately and 12 hours later. If all values were normal, a blood culture was not obtained. If questionable values were obtained at 12 hours, another set of values was obtained 8 to 12 hours later. If abnormal values were found, a blood culture was obtained, the infant was transferred to the NICU, and antibiotics (ampicillin and gentamicin) were started. This was usually because of an increased level of CRP but was occasionally because of an abnormal CBC in association with a clinical finding (eg, mild tachypnea without need for supplemental oxygen).

CBC and CRP were performed in the clinical laboratory, with initial CBC values obtained with a Coulter counter, but differential white blood cell (WBC) counts were individually determined from slides by a laboratory technologist. CRP determinations were performed with a Beckman rate nephelometer and all results were available within 1 hour.

Values were considered to be abnormal if the total WBC count was <5.0 or >30.0 × 10<sup>9</sup>/L, the immature to total neutrophil ratio was >.3, the total neutrophil count was <1.0 × 10<sup>9</sup>/L, or the concentration of CRP was 1.0 mg/dL (10 mg/L) or greater. The limit of detection using the rate nephelometer is currently set at .5 mg/dL.

Duration of antibiotic administration was decided primarily by a return of the serum CRP concentration to <1.0 mg/dL (usually <.5 mg/dL).

## RESULTS

During 1997 and 1998, there were 8299 live births, of whom 7562 were infants who initially went to the well-baby nursery. Of this number, 1894 (25.0%) were evaluated with the clinical pathway for neonatal sepsis. Either because of abnormal clinical features or abnormal laboratory values, 425 infants (22.4% of those evaluated or 5.6% of the total admitted to the well-baby nursery) were transferred to the NICU for further management. The most common reasons for evaluation (risk factors) are listed in Table 1. Transfer to the NICU occurred in 216 infants with risk factors, 206 of whom had abnormal CBC/

CRP (the other 10 had hypoglycemia). The remainder (*n* = 209) had clinical signs, with tachypnea present in 120, oxygen requirement in 90, dyspnea in 56, temperature instability in 19, and apnea in 17 (some infants had >1 finding). Antibiotics were withheld in only 22 cases: in 10 cases because evaluation was for unanticipated hypoglycemia and in 12 cases associated with rapid respiration considered most likely to be secondary to retained fetal lung fluid. None of these 22 infants had an elevated CRP. Details of total WBC, immature/total neutrophil ratio and absolute neutrophil count are not presented, because they did not determine duration of antibiotic therapy.

In 162 cases, antibiotics were given for ~48 hours (some slightly less). Of these, 114 had completely normal CRP concentrations (ie, <1.0 mg/dL) on 3 occasions in a 24- to 36-hour period, and 48 had mild elevations in the first 24 hours (range: 1.0–2.8), which rapidly returned to normal. Some of them had abnormal CBC findings initially. All those with normal CRP concentrations were evaluated for clinical findings, usually tachypnea and/or oxygen requirement and some with unexplained hypoglycemia. Of those with slightly elevated CRP concentrations, maternal fever was most frequently associated (12 cases; 25%). Tachypnea was noted in 7, prolonged rupture of membranes >24 hours in 6, prolonged rupture of membranes >18 hours but <24 hours in 5, mother GBS-positive in 5, hypoglycemia in 5, respiratory distress or oxygen requirement in 5, perinatal depression in 2, and neonatal fever in 1.

The remaining infants were treated for 3 to 5 days in the overwhelming majority of cases, with 6 treated for 6 days, 10 for 7 days (2 with GBS sepsis), and 3 for >7 days (1 with GBS sepsis). As can be seen from Table 2, there was considerable variation in the range of peak CRP concentrations for each duration of treatment, but the mean peak CRP concentrations increased with each day that treatment was needed. In 419 cases, blood culture results proved to be negative and in 6 cases blood culture results were positive within 24 hours. Three grew group B β-hemolytic streptococcus, 2 grew *Staphylococcus epidermidis*, and 1 grew α-hemolytic streptococcus. The 3 infants with GBS sepsis had birth weights of 4250 g, 5785 g, and 2915 g and were investigated because of cyanotic

**TABLE 1.** Major Risk Factors Resulting in Sepsis Evaluation by Clinical Pathway: 1997–1998

Reason for Evaluation	Total Evaluated	Transfer to NICU (%)
35–37 wk gestation	214	12 (5.6)
PROM >18 and <24 h	298	56 (18.8)
PROM >24 h	234	33 (14.1)
Maternal fever*	361	120 (33.2)
Mother GBS-positive	478	40 (8.4)
Hypoglycemia†	225	37 (16.4)

PROM indicates prolonged rupture of membranes.

\* Temperature >38°C, or >38.5°C if epidural analgesia for >6 hours.

† Two or more glucose screening tests <40 mg/dL, confirmed by laboratory test.

**TABLE 2.** Duration of Antibiotic Administration Related to Peak Levels of CRP in Infants Transferred From Well-Baby Nursery to NICU

Duration of Antibiotics	Number	Peak CRP (mg/dL)	
		Mean	Range
None	22	<1.0	
2 d	162 a) 114 b) 48	<1.0	1.0–2.8
3 d	83	2.79	.8–6.0
4 d	85	3.83	.7–8.0
5 d	54	4.34	1.4–7.9
6 d	6	8.37	1.9–11.3
7 d	10	8.90	7.0–13.1
>7 d	3	13.7	8.4–22.9

episodes associated with oxygen desaturation at 11 hours, 6 hours, and 6 hours, respectively. Peak CRP levels in these infants with GBS sepsis were 7.1, 11.5, and 22.9 mg/dL, respectively. One infant who grew *S epidermidis* weighed 2.9 kg at term gestation and developed hypoglycemia. The peak CRP was 2.7 mg/dL and fell to 1.7 mg/dL within 24 hours, at which time, a repeat blood culture result was negative. The leukocyte counts and differential counts were all within normal limits and the infant was treated for 5 days. The other infant with *S epidermidis* had tachypnea but no abnormality of laboratory values and was treated for only 2 days. The infant who grew  $\alpha$ -hemolytic streptococcus weighed 4.2 kg, had slight elevations of temperature with a maximum CRP of 2.5 mg/dL, and was treated for 5 days (the result of a repeat blood culture at 24 hours was negative).

It should be noted that 52 infants of the 7562 admitted to the well-baby nursery were readmitted within 1 month of delivery for evaluation of fever or other suspicion of sepsis. Only 1 of these infants had documented bacterial sepsis or meningitis. This child was admitted at 22 days of age with GBS sepsis and meningitis. His birth weight was 4.45 kg and he was not screened at birth because there were no risk factors for infection, and he was asymptomatic, although the mother's GBS status had not been evaluated. Six infants had documented urinary tract infections, 1 had documented viral meningitis, 1 had pneumonia associated with isolation of an enterovirus, 3 had severe dehydration, 6 had documented respiratory syncytial virus infection, and the rest were presumed to have viral infections. No patient initially treated with antibiotics and discharged when the CRP returned to normal was readmitted within the next month with bacterial infection.

To better understand how the laboratory test results are interpreted and used to make decisions, several illustrative examples are provided in the "Appendix."

## DISCUSSION

Although it is generally acknowledged that neonatal sepsis remains an important diagnostic consideration in the well-baby nursery,<sup>1</sup> making a definitive diagnosis has become more complex in recent years. This is primarily the result of recommendations concerning the prevention of GBS infection,<sup>6</sup> which have resulted in more mothers receiving intrapartum chemoprophylaxis (usually with penicillin or ampicillin).

In nearly all cases in which infants were evaluated because of risk factors during the years of study (1997–1998), antibiotics had been given to the mother, either for preterm labor, for membrane rupture beyond 12 hours, for maternal fever, or because the mother was known to be GBS-positive. Because this may result in a partially treated infant, a clinical pathway for neonatal sepsis was established to evaluate these at-risk infants. During the latter part of 1996, we modified the definition of maternal fever so that infants born to mothers with temperature eleva-

tion to 38.0°C to 38.5°C were not evaluated if epidural anesthesia had been given for >6 hours.<sup>7,8</sup>

The current approach allows a decision about discharge to be made by 24 hours of age and frequently at a little over 12 hours of age. No infant with 2 normal values of CRP and total WBC and differential counts 12 hours apart was readmitted within 1 month of birth with bacterial sepsis or meningitis. There was 1 infant readmitted at 22 days of age with GBS sepsis and meningitis who had no risk factors at birth. We cannot exclude the possibility of readmission elsewhere, but it seems extremely unlikely, because our hospital is the preferred provider for the primary care physicians in this area.

In those infants with abnormal laboratory test results, CRP was the major determinant of duration of antibiotic administration, which then determined the length of stay, in the majority of cases. More than 40% of those transferred to the NICU (184 of 425) were either not treated ( $n = 22$ ) or received antibiotics for only 48 hours ( $n = 162$ ). Another 40% received antibiotics for 3 or 4 days, with a further 14% being treated for 5 days. Very few infants had antibiotic treatment continued beyond 48 hours in face of normal CRP concentrations. Peak CRP primarily dictated duration of antibiotic therapy because high levels (>4 mg/dL) usually take several days to return to normal.<sup>9,10</sup>

CRP rises in response to inflammation or tissue necrosis.<sup>11</sup> Although it is a nonspecific marker, it has been repeatedly shown to increase with bacterial sepsis and meningitis.<sup>1,4,12–14</sup> Consequently, it is difficult to ignore significant elevation of CRP (particularly over 2 mg/dL) and not use antibiotic treatment in the early neonatal period. In some cases, the increase in CRP may be secondary to viral infections, although there are nearly no data in newborn infants concerning this topic. However, in older infants, increases in CRP were associated with several respiratory viruses (adenoviruses, influenza virus, and respiratory syncytial virus).<sup>15</sup>

Clearly, there has been some evolution in the duration of antibiotic administration in infants investigated in the well-baby nursery. A little over 20 years ago, in 1 study of newborn nurseries, in hospital A, antibiotics were given to 4.4% of infants but for a median duration of 7 days, whereas in hospital B, antibiotics were given to 10.5% of infants but for a median duration of 3 days.<sup>16</sup> In another study, it was possible to decrease antibiotic use, using a sepsis screen that included a qualitative determination of CRP.<sup>17</sup>

A decade ago, a national survey indicated that there was no consensus regarding the management of asymptomatic term-gestation infants whose mothers had received intrapartum antibiotics.<sup>18</sup> In a scenario in which the mother had a positive cervical culture result for GBS, many neonatologists would have started antibiotics, with >70% using antibiotics if maternal temperature was >38°C or when membranes were ruptured for >12 hours.<sup>18</sup>

The present clinical pathway provides an alternative to the Centers for Disease Control and Prevention strategy for the management of neonates born to

mothers who are GBS-positive and receive intrapartum antimicrobial prophylaxis.<sup>6</sup> Rather than mandating an observation period of at least 48 hours, combined with WBC, differential, and blood culture, a decision may be made within 24 hours, using WBC, differential, and CRP, or clinical manifestations of infection.

A survey published in 1996 indicated that 21.5% of 461 pediatricians would treat an asymptomatic full-term newborn with antibiotics, when the mother was GBS-positive with no other risk factors.<sup>19</sup> This percentage rose to 61.8% in cases with associated risk factors.<sup>19</sup> In our study, only 8.4% of neonates born to GBS-positive mothers were treated with antibiotics.

We also noted in our study that maternal fever as a single risk factor was associated with NICU admission in 33% of cases and when associated with another risk factor (usually positive GBS culture result), resulted in >40% of infants evaluated being transferred to the NICU with abnormal levels of CRP. It was unusual to have an increased level of CRP at initial evaluation, as noted by others,<sup>14,20</sup> indicating a postnatal increase. The overall frequency of antibiotic use was 5.3% (403 of 7562) but the median duration was 3 days (mean: 3.1 days).

Several years ago CRP was proposed as the best supportive criterion for discontinuation of antibiotic therapy by Squire et al,<sup>21</sup> and others have agreed with this idea.<sup>4,20,22,23</sup> Our approach is similar to that proposed recently by Ehl et al,<sup>23</sup> although our report is limited to term or close-to-term infants. Ehl et al<sup>23</sup> compared 2 antibiotic strategies, using a predetermined duration (at least 5 days) versus a CRP-guided duration in term and preterm infants investigated for suspected sepsis. They had a mean duration of antibiotic treatment of 3.7 days in the group in which CRP was used as the guide to treatment.<sup>23</sup> Our mean duration was 3.1 days.

Another recent report from the same group in Germany suggests that adding interleukin-8 determinations to those of CRP may further reduce the number of neonates treated with antibiotics,<sup>24</sup> although this report dealt with NICU admissions.

In individual cases, there may be clinical features that continue to suggest bacterial infection, despite a normal CRP, which results in prolongation of antibiotic therapy. This happened in several cases during the study, but the most striking observation is that <5% of infants were treated for >5 days, and 3 of 19 in this category had GBS sepsis. Despite this, there were no adverse outcomes.

As mentioned previously, it is difficult to be sure in every case that an elevated CRP is indicative of partially treated bacterial infection. Approximately half of the infants treated were asymptomatic, although a few had evidence of hypoglycemia, in addition to abnormal leukocyte counts and elevated CRP levels. It is not clear how many would become sick if left untreated. However, incorporating CRP determinations into decisions about duration of antibiotic therapy may both minimize exposure of neonates to antibiotics and decrease the likelihood of resistant organisms emerging.<sup>25</sup>

## APPENDIX

		Case 1 (1150)*				
Date		WBC	P	Bands	CRP	
January 17, 1998	6 PM	19.7	58	2	<.4	
January 18, 1998	6 AM	24.8	57	4	<.4	

P indicates polymorphonuclear leukocytes.

\* Risk factors: born at 36 weeks' gestation; prolonged rupture of membranes, 26 hours; and birth weight, 2150 g. Developed hypoglycemia and went to NICU for intravenous dextrose. Evaluated for risk factors; CBC/CRP normal at birth and 12 hours later—not treated with antibiotics.

		Case 2 (0555)*						
Date		WBC	P	Bands	I/T	CRP	Glucose	
January 8, 1998	9 PM	7.7	33	15	.31	<.4	19	
January 9, 1998	9 AM	34.0	69	17	.20	1.9†		
January 10, 1998	6 AM	28.9	73	12	.14	4.7		
January 11, 1998						1.6		
January 12, 1998						.5		

P indicates polymorphonuclear leukocytes; I/T, immature/total neutrophil ratio.

\* Born January 8, 1998, birth weight of 3600 g at 38 weeks' gestation; no risk factors; developed low glucose, so CBC/CRP determined. Glucose responded to early feeds.

† Went to NICU. Blood culture negative. Antibiotics given for 3 days.

		Case 3 (0874)*					
Date		WBC	P	Bands	I/T	CRP	
January 13, 1998	2 PM	17.0	67	4	.06	<.4	
January 14, 1998	2 AM	20.3	79	5	.06	.7	
January 14, 1998	9 AM	15.7	77	3	.04	3.5†	
January 15, 1998	6 AM	12.9	60	0		2.7	
January 17, 1998	6 AM					.4	

P indicates polymorphonuclear leukocytes; I/T, immature/total neutrophil ratio.

\* Born January 13, 1998, birth weight of 2630 g at 41 weeks' gestation. Born by cesarean section (arrest of descent), mother GBS-positive, received antibiotics. CBC/CRP repeated on 1/14 because of slight rise in CRP at 12 hours.

† Went to NICU. Blood culture negative. Antibiotics given for 3 days.

		Case 4 (3566)*					
Date		WBC	P	Bands	I/T	CRP	
February 25, 1998	9 AM	35.0	53	19	.26	<.4	
February 25, 1998	5 PM	30.9	72	17	.19	2.4†	
February 26, 1998	6 AM	28.6	62	22	.26	4.4	
February 27, 1998	6 AM	22.8	83	1	.01	1.5	
February 28, 1998	8 AM					.5	

P indicates polymorphonuclear leukocytes; I/T, immature/total neutrophil ratio.

\* Delivery by cesarean section for arrest of descent. Mother febrile (102°F) and received prenatal antibiotics; birth weight of 3370 g at 42 weeks.

† Went to NICU. Blood culture negative. Antibiotics given for 3 days.

		Case 5 (4332)*					
Date		WBC	P	Bands	I/T	CRP	
March 9, 1998	4 AM	20.0	55	16	.23	<.4	
March 10, 1998	7 AM	20.6	58	4	.06	1.0	
March 11, 1998	6 AM					.5	

P indicates polymorphonuclear leukocytes; I/T, immature/total neutrophil ratio.

\* Born at 41 weeks' gestation; maternal fever not reported; birth weight of 3487 g, March 9, 1998 at 2:05 AM. Developed tachypnea, fever to 101.7°F at birth and oxygen desaturation; admitted to NICU; blood culture sent at 4 AM. Chest radiograph consistent

with retained fetal lung fluid. Blood culture negative. Tachypnea resolved within 12 hours. Antibiotics given for 2 days.

Date	Case 6 (8353)*						
	WBC	P	Bands	I/T	CRP	Glucose	
May 9, 1998 10 AM	12.8	31	22	.42	<.4	42	
May 9, 1998 6 PM	16.4	74	9	.11	1.7		
May 10, 1998 6 AM	31.9	52	24	.32	7.1		
May 12, 1998					1.4		
May 15, 1998					<.4		

P indicates polymorphonuclear leukocytes; I/T, immature/total neutrophil ratio.

\* Term gestation; birth weight, 4250 g; born on May 9, 1998 at 5:14 AM; prolonged rupture of membranes, 16 hours; admission temperature, 101.3°F; oxygen desaturation, tachypnea, and retracting at 11 hours; admitted to NICU. Blood culture at 11 hours was positive for GBS; repeat blood culture and cerebrospinal fluid culture negative on May 10, 1998. Chest radiograph—right lower lobe infiltrates; oxygen supplementation for 12 hours; antibiotics given for 7 days.

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